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09/161,680	09/28/1998	UWE BORNSCHEUER	48429	7944

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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/161,680
Filing Date: September 28, 1998
Appellant(s): BORNSCHEUER ET AL.

Daniel S. Kim
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 4, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 12-27 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 C.F.R. § 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 20 and 26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specific terms that are considered unclear are "*Pseudomonas cepacia* lipase AH", "acylase", and "*Candida antarctica* lipase A" as set forth clearly in paragraph 10 of the Office action mailed March 3, 2004.

Claims 12-27 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is completely set forth in paragraph 12 of the Office action mailed March 3, 2004. In summary, the instant claims are drawn to generating new enzymes using *any* enzyme and *any* substrate to produce a new enzyme (mutated with respect to the original enzyme) with altered substrate specificity relative to the original. The specification provides a single example of such enzymes and substrates that does not support the claimed genus of methods because no correlation between the structures and functions of the reagents used in the methods is described.

Claims 12-27 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for specific examples of the methods proven to achieve their goals, does not reasonably provide enablement for methods using all enzymes, all substrates, and all possible mutator strains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The rejection is completely set forth in paragraph 13 of the Office action mailed March 3, 2004. In summary, the generation of new enzymes is not predictable despite the fact that the experimentation may be routine due to the extensive knowledge in the field of enzymology.

Claims 24-27 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The concept of using this method to generate a "new catalytic activity ...within the same International Union of Biochemistry class as the enzyme's original activity" is not found in the specification as originally filed as set forth clearly in paragraph 14 of the Office action mailed March 3, 2004.

(11) Response to Argument

Appellant argues an objection to the specification (see page 5 of Brief). Said arguments are not addressed herein because objections to the specification are not appealable.

Appellant argues the rejection of Claims 20 and 26 under 35 U.S.C. § 112, second paragraph, as being indefinite. As noted above, the specific terms that are considered unclear are "*Pseudomonas cepacia* lipase AH", "acylase", and "*Candida antarctica* lipase A". Appellant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Appellant argues that Lipase PS and Lipase AH are "art-recognized portions of trade names under which certain lipases from *Pseudomonas candida* [sic] are sold by Amano Enzyme, Inc." and that from this and "the relevant literature, what is meant by '*Pseudomonas cepacia* lipase PS' and '*Pseudomonas lipase* AH' would be abundantly clear to the skilled artisan" (the "*candida*" reference by Appellant is likely a typographical error and should be ---*cepacia*---). The Examiner disagrees with respect to *Pseudomonas lipase* AH (as set forth clearly in paragraph 10 of the Office action mailed March 3, 2004, the rejection of the lipase PS has been

withdrawn). The definition of the "AH" enzyme is not clear in the prior art. No attachments filed by Appellant have set this forth clearly. The Examiner refers to a lack of an entry for *Pseudomonas lipase* AH in the Registry file, which is "[t]he largest and most current database of chemical substance information in the world containing more than 24 million organic and inorganic substances and 48 million sequences" (see http://www.cas.org/EO/regsys.html). Thus, while the abbreviation PS clearly indicates the Amano enzyme referred to be Appellant in the specification and their arguments, this is not the case for the AH enzyme. Moreover, the Examiner maintains that limitations, such as using only those enzymes listed in Table 1, can be read into the claims. No reference to Table 1 has been inserted into the claims as suggested by the Examiner (see paragraph 10 of the Office action mailed March 3, 2004).

Additionally, Appellant does not argue that the terms "acylase" and "*Candida antarctica* lipase A" are considered indefinite in paragraph 10 of the Office action mailed March 3, 2004. The Examiner maintains the rejection as previously set forth.

Appellant argues the rejection of Claims 12-27 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Appellant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Appellant argues that production of functional derivatives of the mutator strain would be "obvious and straightforward" given the level of skill in the art. This is not found persuasive because what is noted as lacking adequate written description is not functional derivatives of the mutator strain but all enzymes and all the possible new substrates to be tested as alternative

substrates (i.e., the new catalytic activity). As reiterated from paragraph 12 of the Office action mailed March 3, 2004:

"The instant claims are directed to methods altering an enzyme's substrate specificity using (1) a random mutator strain, (2) a gene for the unmutated enzyme, (3) a new, desired substrate for the enzyme, and (4) a screening procedure…

The instant claims are drawn to using *any* enzyme and *any* new substrate to produce a new enzyme with altered substrate specificity relative to the original. The specification provides a *single* example of such enzymes and substrates and no correlations between their structures and functions. The field of enzymology is enormous with six major enzyme categories (provided by the Enzyme Commission in the form of E.C. numbers) and numerous subdivisions within each category based on the functionality of each enzyme. For example, how different from the typical esterase substrate can you get and still practice the claimed method effectively? Is there any correlation between how different the substrate and how many rounds of mutagenesis are necessary to achieve the desired goal? Are there occasions that, structurally, the method will not work? Considering all these questions, it is clear that the written description of a single example in the instant specification does not adequately describe the genus of "reagents" claimed for use in the methods.

A method is unable to be practiced without a complete description of the reagents used in that method. Since the invention is claimed in such broad and inexact terms, written description for the genera noted is required so that one of skill in the art would recognize Appellants were in possession of the claimed invention. That is not the case here considering the lack of description for the field of enzymology."

The Examiner further notes that the decision in *University of Rochester v. G.D. Searle & Co.* (69 USPQ2d 1886 (2004)) that specifically points to the applicability of decisions in both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. A product, used in the claimed methods, must have adequate written description of (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed as iterated in *Enzo Biochemical.*

Appellant argues the rejection of Claims 12-27 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for specific examples of the methods proven to achieve their goals, does not reasonably provide enablement for methods using all enzymes, all substrates, and all possible mutator strains. Appellant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Appellant argues that the nature of the experimentation required would be routine for a skilled artisan. The Examiner disagrees. Despite the extensive skill in the field of enzymology, being "routine" requires a predictable outcome. In the instant case, the fact that a "new catalytic activity" can be produced is simply not predictable. Enzymes have specific characteristics (amino acid residues) in their catalytic "active" sites to perform a specific chemical reaction, such as forming a C-C bond; such characteristics cannot be predictably altered to now catalyze a hydration reaction (adding H_2O to a C=C bond), for example. Thus, while enzyme assays that

monitor an enzyme's known catalytic activity are considered routine in the art, monitoring *new* enzyme activities with *new* substrates and randomly mutated (*new*) enzymes is in no way routine due to the lack of predictability, among other Wands factors (see paragraph 13 of the Office action mailed March 3, 2004 for a complete Wands analysis).

Appellant argues that determining "how divergent" the new substrate can be from the original substrate is plainly recognizable. The Examiner disagrees. To investigate the tolerance of a specific enzyme to mutations for the purpose of altering the enzyme's activity (substrate usage and catalytic activity performed) is highly specific to the enzyme used. Again, the field of enzymology is well developed, but alterations of enzymes are highly case (enzyme) specific. The specification presents no guidance about such tolerance or about enzyme specificity in general. The process claimed is use of a known mutator strain to randomly mutagenize enzymes and randomly check for new enzyme activities by screening wherein the predictability of finding new enzyme activities is extremely low.

Appellant argues the rejection of Claims 24-27 under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. Appellant's arguments have been fully considered but are not deemed persuasive for the following reasons. Appellant argues that the concept of using the claimed method to generate a "new catalytic activity ...**within the same International Union of Biochemistry class as the enzyme's original activity**" (emphasis added) is supported on page 4, line 10 and from the example beginning on page 11. The Examiner disagrees.

From the specification around Appellant's citation on page 4:

"It is possible in principle for the substrate specificity of all enzymes to be altered, and preferably the substrate specificity of hydrolases altered in the novel method. Hydrolases form the 3rd class of enzyme (= 3..) in the IUB nomenclature system. Hydrolases are preferred in the novel method because, as a rule, a simple detection reaction for them exists and, in many cases, they are used in industrial syntheses."

From the specification concerning the example beginning on page 11: An esterase gene was used; the non-mutated PFE gene product converts ethyl acetate into acetic acid (see page 11, item 2) whose production can be measured by pH or color (when indicators are present). PFE was randomly mutated in the mutator strain *E. coli* XL1 Red without any particular (substrate) additions to the "mutating" media (see page 13, item 5). The randomly mutated PFE gene was then screened using a variety of unspecified substrates (see page 12, item 4 and pages 13-14, item 7), presumably this variety included compound 1 because a resulting "new" activity is described on page 16 as hydrolyzing compound 1. Nowhere in this example is it stated that the new enzyme screened for must be of the same IUB classification; IUB classification is not mentioned.

Thus, the Examiner disagrees that either citation provided by Appellant supports the amendment.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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October 14, 2004

Conferees

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